Claim Rejection-35 U.S.C § 112

The Examiner has rejected claims 33 and 34 under the first paragraph of 35 U.S.C. § 112 for not meeting the written description requirement. The Examiner asserts that the subject matter of these claims ("for more than 36 hours" in claim 33 and "for more than 36 hours at 0.5-12°C" in claim 34) was not detailed in the specification in a manner conveying possession of the claimed subject matter. Applicants respectfully disagree with this rejection. The Examiner's attention is directed to pages 22 and 28 of the specification. On page 22 of the specification, Applicants define "improved preservation solution" as being a liquid that stores organs or tissues for a long time, e.g. up to 36 hours or more (lines 8-10 on page 22 of the specification). As such, the "for more than 36 hours" feature is provided with adequate written description and conforming with the requirements 35 U.S.C. § 112. Furthermore, the temperature range detailed in claim 34 is supported by the written description appearing on page 28 of the specification where it is explained that "0.5-12°C, preferably 2-8°C, and more preferably 4°C, has been found to be most advantageous" for long term preservation.

Applicants have amended claims 33 and 34 to be more consistent with the above referenced disclosure. Most notably, these claims now detail "36 hours or more" instead of the phrase "for more than 36 hours". The amended phrase is detailed in the specification and would not be considered new matter. Applicants request that these rejections be withdrawn.

* * *

Claims 1, 5-7, 24-32 are rejected as indefinite under the second paragraph of 35 U.S.C. § 112.

Claims 1 and 5 have been amended to delete "improved". Claim 5 has been further amended to delete the word "optionally".

Regarding the rejection of claim 6, Applicants have provided the following comments regarding THAM buffers. In human blood, there are several different compounds that have different buffer actions. The present invention utilizes the several buffers to imitate human blood. THAM (Tris hydroxymethylaminomethane, also called tromethamol) buffers have extracelleuar and intracelleur buffering activity. The phosphate buffer, on the other hand, has mainly an extracelleuar buffering action and is similar to natural phosphate buffers present in blood.

Claim 26 has been amended to correct the typographical error.

Claim 31 has been amended by replacing "exposing" to "placing".

Claim 32 has been amended to identify that it pertains to a "method for preserving vascular endothelium".

Claims 33 and 34 are asserted to be definite. The claims detail that the storage time is 36 or more. This claim may be broad, but it is definite. Applicants have amended these claims to add the "0" to "0.5".

Applicants respectfully assert that the above amendments and comments obviate the rejections detailed in the Office Action.

Claim Rejection-35 U.S.C § 103

Claims 5, 7, 24-29, and 31-34 are rejected as obvious based upon Walkenbach [IDS-12, AO, 1991] in combination with Ingemansson I [IDS-12, AN, 1995] and Ingemansson II [IDS-1, AT-2, 1995].

Claim 5 has been amended to remove "optionally" in front of "nitroglycerin" to clarify the subject matter of the invention. None of the cited prior art discloses the use of nitroglycerin in a preservation solution. As such, Applicants respectfully submit that the obviousness rejection of independent claim 5 should be withdrawn. Furthermore, Applicants submit that the rejection of dependant claims 7, 7, 24-29, and 31-34 should also be withdrawn.

* * *

Claims 1, 5-7, 24-34 are rejected as obvious based upon Walkenbach [IDS-12, AO, 1991] in combination with Ingemansson I [IDS-12, AN, 1995] and Ingemansson II [IDS-1, AT-2, 1995] in further view of Pinsky [IDS-1, AQ-2, 1994] and Naka [IDS-1, AT-1, 1995].

The Examiner acknowledges that Walkenbach, Ingemansson I, and Ingemansson II fail to disclose the nitroglycerin feature. The Examiner attempts to alleviate this failing based upon the teachings of Pinsky and Naka. The Examiner suggests that the motivation for the proposed combination is based on the belief that nitroglycerin was known to enhance survival of animal tissue and maintained vascular homeostasis.

Applicants have amended independent claims 1 and 5 to specify that the organs, tissues, and parts thereof contain endothelium. Support for this amendment can be found on pages 16 and 17. This amendment was done to clarify the subject matter of the claimed invention.

Applicants provide the following comments for the Examiner's consideration.

The Walkenbach document discloses a preservation solution for the preservation of the cornea and does not include nitroglycerin (as noted by the Examiner). Nothing is disclosed regarding preservation of other organs and tissues including vascular endothelium, e.g. blood vessels and/or contractile tissues. The anatomy and physiology for the cornea differs substantially from that of other organs. The cornea does not include any blood vessels and thus

has no endothelium. The calcium present in the Walkenbach preservation solution therefore could not be relied upon for disclosure pertaining to other tissues. The calcium is merely present in a conventional cornea preservation solution. The Walkenbach document would never be considered by a person skilled in the art as directed to the problem behind the present invention, i.e. to improve as many biological functions as possible in organs and tissues or parts thereof. The Walkenbach document only focuses on the preservation of the cornea and there would be no motivation to combine its teachings with those relating to other organs and tissues.

The Ingemansson I document, published in May 1995, is titled "Long-term preservation of vascular endothelium and smooth muscle", and it is suggested in the last sentence of the initial abstract (in bold text) that addition of calcium to UW and Perfadex might improve their ability to preserve smooth muscle function during prolonged storage. In the experiments disclosed in the Ingemansson I article, performed on infrarenal aortas of rats, the only solution tested containing calcium was Krebs solution. Advantageous results were obtained after preservation of the smooth muscle function of the aortas during prolonged storage. Therefore, the editors suggest addition of calcium of UW and Perfadex solutions for the preservation of smooth muscle function. However, as disclosed in column 2, lines 4-7, the use of calcium in the Krebs solution induced a marked decrease in EDRF (endothelium-dependent relaxing factor) function. Thus, the presence of calcium in this solution has unsatisfactory, in practice a detrimental, effect on the aorta endothelium during long-term preservation.

In contrast, according to the present invention improved long-term preservation of both the smooth muscle and the endothelium of organs and tissues containing endothelium, e.g. blood vessels, is aimed and obtained. As the Ingemansson I reference clearly discloses, the addition of calcium has an unsatisfactory effect on endothelial relaxation. The Ingemansson I document

teaches away from the present invention. Further, nothing about nitroglycerin is disclosed in this document.

As disclosed in the description (page 6, line 27, to page 7, line 18) and as argued in previous responses to Office Actions in the present case, the unique vascular endothelium preserving effect of calcium has not been known before the priority date of the present application. Further, due to the well known calcium paradox (see page 2, second paragraph, in the Declaration filed in February 2000), i.e. organs perfused with an extra cellular solution for a while and then with the same solution, but now including calcium, may be destroyed quicker when perfused with a calcium containing solution due to an detrimental increase of the intracellular calcium content, it has for a long time been, also at the priority date of the present application, and still is, a general concept among persons skilled in the art that calcium should not be present in genuine preservation solutions for transplants including vascular endothelium. The two most common organ preservation solutions in clinical use worldwide today are UW and Euro-Collins solutions, neither of them contain calcium.

Thus, at the priority date of the present application nothing had previously been published about advantageous effects of calcium on the endothelium of organs during long-term preservation.

Moreover, nothing is disclosed or suggested about any combination of calcium and nitroglycerin in such a solution, which would give the surprising synergistic effect obtained with the present invention.

Therefore, the Walkenbach and Ingemansson I documents must be regarded as irrelevant and would not be considered by a person skilled in the art aiming to solve the problem behind the

present invention. In particular the Ingemansson I documents teaches away from the present invention.

The Ingemansson II reference, disclosing the known Perfadex solution, does not describe or suggest calcium and/or nitroglycerin as ingredients in a preservation solution. This reference only relates to the state of the art and would not alleviate any of the failings of the primary reference.

Before discussing the Pinsky and Naka references, the term "genuine preservation" should be defined again. It is of great importance to distinguish between genuine preservation solutions and wash, irrigation and infusion solutions. The latter are sometimes wrongly referred to as preservation solutions in the literature. As the one skilled in the art recognizes, one of today's requirements made on a genuine organ preservation solution is that it has to provide a substrate for metabolism. Further, it has to be hyperosmolar, thereby preventing cell oedema when lowering the organ temperature. It should also contain big molecules which gives the solution colloidosmotic pressure, thereby making it possible to perfuse organs without creation of tissue oedema. Also, it has to contain buffers and other beneficial substances with a view to preventing the harmful effects of ischemic metabolites arising during the preservation.

The Office Action alleges that Pinsky or Naka discloses that nitroglycerine maintains vascular homeostasis, which nitroglycerine can be added to known perfusion solutions such as lactated Ringer's solution. Nitroglycerine is added to a different type of solution according to the present invention, and for a different purpose than the solutions in Naka or Pinsky.

First, with regard to the purpose of nitroglycerine, Applicants respectfully submit that the advantageous results of adding nitroglycerine to a Perfadex solution was not suggested in Naka or Pinsky which merely described maintaining vascular homeostasis. Page 8, lines 18-23 of the

present specification describes the unexpected benefit of promoting endothelium dependent relating factor (EDRF) function by adding nitroglycerine to a LPD preservation solution. No suggestion is found in Naka or Pinsky to add nitroglycerine to a LPD solution. No suggestion is found in Naka or Pinsky to add nitroglycerine to a LPD solution to obtain the unexpectedly advantageous results described above.

Second, with regard to the type of solutions, the presently claimed invention does not combine nitroglycerine with Ringer's solution (which does not contain a colloidosmotically active substance), but rather combines nitroglycerine with a solution containing a colloidosmotically active substance, such as a Perfadex solution. Applicants respectfully submit that there is no teaching, suggestion, or motivation in Pinsky or Naka that suggests that there will be a reasonable expectation of success of improving smooth muscle function and endothelial function if nitroglycerine in Ringer's solution (which does not contain a colloidosmotically active substance) is added to a solution containing a colloidosmotically active substance. Although, Perfadex solution alone will not itself maintain smooth muscle function and endothelial function in blood vessels, such expectation is not found due, in part, to the differences in Ringer's solution and the solution of the claimed invention, which is discussed below in more detail.

The present specification discusses the differences in a solution such as Ringer's solution, which lacks a colloidosmotically active substance, and the preservation solution of the present invention, which contains such a substance. Please see the present specification on pages 3-5. Ringer's solution as disclosed in Naka and Pinsky are not satisfactory for long-term preservation solutions and thus are not satisfactory for maintaining smooth muscle function and endothelial function in blood vessels. Please see the present specification, page 4, lines 10-13. Further,

evidence that Ringer's solution is not a long-term preservation solution is found in the results on page 207 of Naka, that show that lungs preserved for 4 hours in Ringer's solution had a 0% recipient survival rate. Please see Naka, first line under "Results" and last sentence of second paragraph under "Results".

Due to the foregoing, Applicants submit that the invention detailed in claims 1 and 5 would not be obvious based upon the cited prior art. The cited prior art fails to provide for all of the claimed features and there is not sufficient motivation for the proposed combinations. The rejection of independent claims 1 and 5 and the resulting dependant claims should be withdrawn.

CONCLUSION

Applicants respectfully requests allowance of the application. If any additional fees are due in connection with the filing of this response, such as fees under 37 C.F.R. §§ 1.16 or 1.17, please charge the fees to Deposit Account No. 02-4300. Any overpayment can be credited to Deposit Account No. 02-4300.

Respectfully submitted,

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* Practice is limited to matters and proceeding before federal courts and agencies.

1. (Amended) [An improved] A preservation solution for organs and tissues or parts thereof from humans and animals containing endothelium, comprising:

calcium ion,

at least one colloidosmotically active substance, and

nitroglycerin.

5. (Amended) [An improved] A preservation solution for organs and tissues or parts thereof from humans and animals containing endothelium, comprising:

calcium ion,

[optionally] nitroglycerin,

about 1-15% by weight low-molecular dextran having an average molecular weight of about 1,000 daltons,

about 3-8% by weight high-molecular dextran having an average molecular weight of 40,000 - 120,000 daltons as a colloidosmotically active substance,

about 0.1 - 2.6% glucose as a substrate,

buffer,

about 4-25 mM potassium ions,

about 1-16 mM magnesium ions,

about 50-150 mM sodium ions, and about 50-150 mM chloride ions,

wherein the amounts are based on the final volume of the improved preservation solution.

26. (Amended) The method of preserving organs and tissues or parts thereof from humans or animals according to claim 24, wherein said tissue is vena [sapena] saphena magna or parts thereof.

31. (Amended) A method for maintaining the integrity of vascular endothelium, comprising:

[exposing] placing said organs, tissues and parts thereof [to] into the preservation solution according to claim 5.

32. (Amended) A method for [maintaining the integrity of] preserving vascular endothelium, comprising:

storing [the] a contractile tissue in the preservation solution according to claim 5,

wherein[:] nitroglycerin is present in an amount of about 10^{-4} - 10^{-7} M; and calcium ion is present in an amount of about 0.3 - 1.5 mM calcium, based on the final volume of preservation solution.

33. (Amended) A method for preserving organs and tissues or parts thereof from humans and animals, comprising:

flushing an organ or a tissue with the improved preservation solution according to claim 1,

immersing the organ or the tissue in the improved preservation solution, and

storing the improved preservation solution containing the organ or the tissue for [more than 36 hours] 36 hours or more at 0.5-12°C.

34. (Amended) A method for preserving organs and tissues or parts thereof from humans and animals, comprising:

flushing an organ or a tissue with the improved preservation solution according to claim 5,

immersing the organ or the tissue in the improved preservation solution, and

storing the improved preservation solution containing the organ or the tissue for [more than 36 hours] <u>36 hours or more</u> at <u>0</u>.5-12°C.